ABSTRACT

Lipohydroxy acid is a derivative of salicylic acid with unique properties that explain its clinical effects in the skin. Lipohydroxy acid has skin renewing, exfoliating, and acne treating properties and is a commonly used ingredient in personal skin care products. The slow penetration of lipohydroxy acid results in an individual cell-by-cell exfoliation that is associated with excellent tolerability. Lipohydroxy acid has been shown to induce dermal thickening by stimulating glycosaminoglycans, collagen, and elastin production. Finally, lipohydroxy acid has been demonstrated to possess comedolytic properties. This article reviews the available data on the use of lipohydroxy acid in treating aging skin and acne.

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REVIEW

The Use of Lipohydroxy Acid in Skin Care and Acne Treatment

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HYDROXY ACIDS (HAs) ARE therapeutically active skin care ingredients with exfoliating and rejuvenating properties. Many are found naturally in botanical sources, hence the name "fruit acids." They are broadly divided into alpha hydroxy acids, beta hydroxy acids, polyhydroxy acids, and bionic acids (e.g., lactobionic acid) based on the position of one or more hydroxyl groups on the molecular structure. HAs possess the exfoliating properties, separating skin cells from the stratum corneum and providing clinical benefits to skin diseases characterized by hyperkeratosis, including acne vulgaris.[1] In addition, many HAs provide antiaging benefits, as they have dermal thickening properties from stimulation of glycosaminoglycans, collagen, and elastin.[2]

While most consider salicylic acid (SA) a member of the beta hydroxy acid family, in reality its chemical structure is different from other members of this family. The acidity of most HAs are determined by the carboxyl group, while the hydroxyl group is neutral. In the case of SA, it is thought by some that an acidic phenolic hydroxyl group is what explains its unique behavior in the skin and makes it unique compared to other HAs.[3] Moreover, unlike most other HAs, the chemical structure of SA renders it soluble in oil rather than water.[4] It is the lipophilicity of SA that enhances its efficacy in treating acne,

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as it can more easily penetrate into the sebum-rich sebaceous gland.

Lipohydroxy acid (LHA), also known as C8-LHA or 2-hydroxy-5-octanoyl benzoic acid, is a SA derivative. With a higher molecular weight and an added fatty chain, it is more lipophilic than SA.[4] These chemical differences result in particular clinical characteristics that make LHA unique in treating the skin. LHA was first developed by L'Oreal researchers in the 1980s, and as such, is found only in L'Oreal brand skin care products.

LIPOHYDROXY ACID: EXFOLIATING AND SKIN RENEWING PROPERTIES

The chemical structure of LHA results in less skin penetration than its parent SA. In fact, with respect to skin penetration, it exhibits a profile similar to glycolic acid. One *in vitro* Franz chamber skin assay revealed only six percent of LHA penetrated past the stratum corneum versus 58 percent of SA.[4,5] *In vivo* tape-strip analysis revealed 17.1 percent of LHA was retained in the stratum corneum after a four-day application period, versus 9.7 percent of SA.[4,6] Hence, there is a larger reservoir effect in the stratum corneum with use of LHA compared to SA.

Many HAs are referred to as having a "keratolytic effect." However, despite this terminology, the process of exfoliation does not actually affect keratin, but rather involves breakage of intercellular desmosomes as corneocytes are shed.[7,8] Both SA and LHA have been shown to enhance corneocyte desquamation, reducing the overall thickness of the stratum corneum.[9–11] However, inherent properties of the two molecules result in different types of exfoliation. While SA penetrates more rapidly into the skin than LHA, desmosomes are also more rapidly broken resulting in exfoliation of sheets of cells.[12] The highly lipophilic properties of LHA, on the other hand, slow its penetration and results in an exfoliation of individual corneosomes.[4,13] This cell-by-cell exfoliation is thought to more closely mimic physiologic desquamation than the more global exfoliation that results from use of SA or other HAs. Whether the LHA's ability to more closely mimick physiologic desquamation results in better tolerance needs continued evaluation.

While LHA use results in stratum corneum thinning, it is also associated with dermal thickening. In one study, the dermal stimulatory effects were found to be equivalent to that of tretinoin.[14] These antiaging effects are thought to be largely due to LHA's stimulation of structural skin proteins and lipids. HAs in general have been shown to increase levels of glycosaminoglycans, hyaluronic acid, collagen, and elastin in the dermis.[2,4] In animal studies, SA has also been shown to stimulate epidermal cell division,[15] and in human skin samples, LHA has been found to increase cell renewal.[16] However, this is controversial with confounding reports in the literature on whether HAs actually stimulate cell division.[4,9,17] The mechanism by which HAs increase cell turnover is theorized to be due to a possible signal from release of lamellar lipids during enhanced desquamation[18] or mechanical forces from the exfoliation having a direct stimulatory effect.[19]

LIPOHYDROXY ACID: COMEDOLYTIC PROPERTIES

Given its extremely lipophilic nature, LHA has a high affinity for the pilosebaceous unit making it an excellent option as a comedolytic agent for acne vulgaris. In one split-face study comparing LHA to no treatment, patients with comedonal acne applied LHA once daily for a month. After treatment, cyanoacrylate skin strips were used to asses the size and density of follicular casts. LHA reduced number of follicular casts by 47 percent ($p<0.01$) and their size by 54 percent ($p<0.01$) compared to the untreated side.[20] Another small study evaluated the twice-daily use of LHA in 14 acne patients. A combination of ultraviolet-light video recording with computerized image analysis evaluated the characteristics of comedones. A significant decrease in the size and number of comedones after use of LHA was reported, reflective of LHA's comedolytic effects. While specific numbers were not published, it appears from graphical data in the paper that there was approximately an 85-percent reduction in follicular plugs from Day 1 to Day 14.[21]

LIPOHYDROXY ACID: DATA IN TREATING ACNE

The United States Food and Drug Administration's (FDA) acne monograph permits over-the-counter (OTC) products to claim acne treatment benefits if they contain benzoyl peroxide (BPO), SA, or sulfur as single active ingredients.[22] Despite being related to SA, LHA is a distinct molecule and is not included in the FDA acne monograph. Therefore, efficacy in treating acne from any OTC product containing LHA must be attributable to one of the three previously listed ingredients and is independent of LHA. Despite this, there are data on the use of products containing LHA in treating acne.

One study has evaluated LHA monotherapy compared to BPO in treating acne. LHA demonstrated comparable efficacy and greater tolerability compared to BPO, and the authors concluded that LHA could serve as an option for those acne patients intolerant of BPO.[23] Another study evaluated an OTC fixed-dose combination of 5.5% BPO with LHA. In the multicenter, double-blind study, OTC BPO 5.5%-LHA in combination with with prescription tretinoin cream 0.025% was compared to prescription fixed-dose combination BPO 5%-clindamycin 1% gel along with the same prescription tretinoin cream 0.025%.[24]

In the study, subjects were randomized into one of the two arms and applied one of the fixed-dose products in the morning and the tretinoin cream in the evening. Sixty-six patients, ages 18 to 50 years, with mild-to-moderate acne participated in the 12-week study across three United States study centers. Clinical efficacy variables included acne lesion counts as well as overall skin appearance, including tone and texture. Safety and tolerability of the regimens were also evaluated.[24]

Both acne regimens demonstrated statistically significant improvement in global acne assessment as well as skin tone, smoothness, brightness, appearance of pores, and overall appearance at Weeks 4, 8, and 12 compared to baseline ($p<0.05$). Comedonal, inflammatory, and total lesion count reductions were similar in both groups at Weeks 4, 8, and 12 and statistically better than baseline lesion counts ($p<0.05$). Both treatments resulted in skin dryness and peeling at early time points, as expected during the initial skin retinization period. At Week 2, however, there was statistically more skin erythema in fixed-dose combination BPO-clindamycin ($p=0.042$) gel arm, which was not observed in the BPO-LHA arm. Otherwise, there were no differences in investigator- or subject-reported tolerability between the treatment arms.[24]

As part of a combination regimen with topical tretinoin 0.025% cream, BPO 5.5%-LHA was as effective as BPO 5%-clindamycin 1% gel in treating mild-to-moderate acne. BPO 5.5%-LHA also demonstrated statistically less erythema and the Week 2 time point compared to the BPO 5%-clindamycin gel arm. In the real world, better tolerability may translate to improved medication adherence and ultimately better clinical outcomes. According to the FDA monograph, claims for efficacy in treating acne can only be attributed to the BPO component of this product. However, given the known comedolytic and keratolytic properties of LHA,[9–11,21] it may help enhance the effect of BPO and contribute to the results observed in the study.[24]

CONCLUSION

LHA is a SA derivative with skin-renewing, keratolytic, and comedolytic properties. Its unique structure offers a physiologic, cell-by-cell exfoliation and enhanced tolerability as compared to its cousin SA. As an anti-aging ingredient, LHA use has been shown to result in dermal thickening, with increases in glycosaminoglycan, hyaluronic acid, collagen, and elastin levels. Its comedolytic properties have been shown *in vitro*. As an acne monotherapy, LHA has been demonstrated to be on par with BPO in one study. As part of a fixed-dose combination, LHA, along with BPO, has been clinically evaluated and proven to be as effective with a more favorable tolerability profile in comparison to prescription BPO 5%-clindamcyin as part of a regimen with prescription tretinoin 0.025% cream.

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